

FORM PTO-1390  
(REV 11-98)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER

TRANSMITTAL LETTER TO THE UNITED STATES  
DESIGNATED/ELECTED OFFICE (DO/EO/US)  
CONCERNING A FILING UNDER 35 U.S.C. 371

U.S. APPLICATION NO. (If known, see 37 CFR 1.51)

09/647330

INTERNATIONAL APPLICATION NO.

PCT/GB99/00967

INTERNATIONAL FILING DATE

March 26, 1999

PRIORITY DATE CLAIMED

March 27, 1998

TITLE OF INVENTION

POLYMORPHISM III: LINKAGE OF ATOPY TO A LOCUS ON CHROMOSOME 13

APPLICANT(S) FOR DO/EO/US WILLIAM OSMOND CHARLES MICHAEL COOKSON; SUMIT BHATTACHARYYA;  
NICHOLAS LEAVES

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
  - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☒ has been transmitted by the International Bureau.
  - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
  - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☐ have been transmitted by the International Bureau.
  - c. ☐ have not been made, however, the time limit for making such amendments has NOT expired.
  - d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A **FIRST** preliminary amendment.  
☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:  
Courtesy copy of published PCT application

422 Rec'd PCT/PTO 27 SEP 2000

U.S. APPLICATION NO. (if known) 37 CFR 1.51 <b>09/647330</b>		INTERNATIONAL APPLICATION NO. PCT/GB99/00967		ATTORNEY'S DOCKET NUMBER	
17. <input type="checkbox"/> The following fees are submitted: BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)): Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO ..... \$970.00 International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO ..... \$840.00 International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... \$760.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) ..... \$670.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) ..... \$96.00 <b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b>				CALCULATIONS PTO USE ONLY \$ 840	
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				\$	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	14 - 20 =		X \$18.00	\$	
Independent claims	2 - 3 =		X \$78.00	\$	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ \$260.00	\$	
<b>TOTAL OF ABOVE CALCULATIONS =</b>				\$ 840	
Reduction of 1/2 for filing by small entity, if applicable. A Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).				\$	
<b>SUBTOTAL =</b>				\$	
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				\$	
<b>TOTAL NATIONAL FEE =</b>				\$ 840	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property +				\$	
<b>TOTAL FEES ENCLOSED =</b>				\$ 840	
				Amount to be:	\$
				refunded	\$
				charged	\$

- a. ☐ A check in the amount of \$\_\_\_\_\_ to cover the above fees is enclosed.
- b. ☒ Please charge my Deposit Account No. 20-1430 in the amount of \$ 840 to cover the above fees. A duplicate copy of this sheet is enclosed.
- c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 20-1430. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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37,505

REGISTRATION NUMBER

430 Rec'd PCT/PTO 27 SEP 2000

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. National Phase of

PCT/GB99/00967 of:

William Osmond Charles Michael  
Cookson et al.

Application No.: Unassigned

Filed: Herewith

For: POLYMORPHISM III: LINKAGE  
OF ATOPY TO A LOCUS ON  
CHROMOSOME 13PRELIMINARY AMENDMENT

Box PCT

Assistant Commissioner for Patents

Washington, D.C. 20231

Sir:

Prior to examination of the above-referenced application, please enter the following amendments and remarks.

IN THE CLAIMS:

Please amend claims 5, 6, 7, 8, 12 and 14 as follows. All pending unamended claims have been reproduced in small type for ease of reference.

1. (Amended under Article 34) A method for diagnosing an individual as being atopic, or as having a predisposition to atopy, which method comprises demonstrating in a nucleic acid sample taken from an individual the presence or absence of an allele which is associated with atopy, wherein the allele is situated at a locus in a region of chromosome 13 of up to 1 megabase in length, which region contains the locus D13S273, the presence of the allele D13S273\*4 being indicative of a predisposition to asthma.

2. (As filed) The method according to claim 1, wherein the method comprises the steps of:

- (i) obtaining a suitable tissue sample from the individual;
- (ii) preparing from the tissue sample a nucleic acid sample;
- (iii) analyzing the nucleic acid sample for the presence or absence of the allele.

1                   3.       (As filed) The method according to claim 2, wherein prior to analysis, the locus at  
2 which the allele is situated is amplified.

1                   4.       (As filed) The method according to claim 3, wherein the amplification is by the PCR.

1                   5.       (Amended) The method according to [any one of the] claim[s] 1 [to 4],  
2 wherein the locus at which the allele is situated comprises microsatellite repeats of variable  
3 lengths.

1                   6.       (Amended) The method according to claim 4 [or claim 5], wherein  
2 amplification is performed using a pair of primers each of which hybridize under suitably  
3 stringent conditions to a region either side of the microsatellite repeats.

1                   7.       (Amended) The method according to [any of] claim[s] 1 [to 6], wherein  
2 the allele for identification is D13S273\*4.

1                   8.       (Amended) The method according to [any one of] claim[s] 3 [to 7],  
2 wherein the analysis is carried out by size separation of amplification products.

1                   9.       (As filed) The method according to claim 7, wherein the primers in the pair of primers  
2 comprise the oligonucleotide sequences identified by SEQ ID NO: 1 and SEQ ID NO: 2 or substantially similar  
3 sequences.

1                   10.      (As filed) A pair of oligonucleotide primers for amplification of an allele which is  
2 associated with atopy, which allele is situated at a locus in a region of chromosome 13 of up to 1 megabase in  
3 length, which region contains the locus D13S273, but not including the region containing the locus D13S153.

1                   11.      (As filed) The pair of oligonucleotide primers according to claim 10, one of which is  
2 labeled with a detectable marker.

1                   12.      (Amended) The pair of oligonucleotides according to claim 10 [or  
2 claim 11] capable of hybridizing under suitable stringent conditions to a region either side of a  
3 region of microsatellite repeats at D13S273.

1                   13.       (Amended under Article 34) The pair of oligonucleotide primers according to  
2 claim 12, comprising the oligonucleotide sequences identified by SEQ ID NO: 1 and SEQ ID NO: 2 or similar  
3 sequences.

1                   14.       (Amended) An assay kit which comprises the pair of oligonucleotide  
2 primers according to [any one of] claim[s] 10 [to 13].


REMARKS

Amendments to claims 5, 6, 7, 8, 12 and 14 have been made to remove multiple  
claim dependency.

CONCLUSION

If the Examiner believes a telephone conference would expedite prosecution of  
this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

  
Joe Liebeschuetz  
Reg. No. 37,505

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POLYMORPHISM III: LINKAGE OF ATOPY TO A LOCUS ON CHROMOSOME 13

This invention is concerned with methods for the diagnosis of  
5 atopic disease and with materials and methods relating thereto.

Atopy is a tendency to develop high levels of IgE and immediate hypersensitivity to allergens. Atopic diseases include hay fever, infantile eczema and most forms of asthma. Asthma is a disease which is becoming more prevalent and is the most common disease of childhood (1). Most  
10 asthma in children and young adults is initiated by IgE mediated allergy (atopy) to inhaled allergens such as house dust mite and cat dander. However, not all asthmatics are atopic, and most atopic individuals do not have asthma, so that factors in addition to atopy are necessary to induce the disease (2,3). Asthma is strongly familial, and is due to the interaction  
15 between genetic and environmental factors. The genetic factors are thought to be variants of normal genes ("polymorphisms") which alter their function to predispose to asthma.

Asthma may be identified by recurrent wheeze and intermittent air flow limitation. An asthmatic tendency may be quantified by the  
20 measurement of bronchial hyper-responsiveness in which an individual's dose-response curve to a broncho-constrictor such as histamine or methacholine is constructed. The curve is commonly summarised by the dose which results in a 20% fall in air flow (PD20) or the slope of the curve between the initial air flow measurement and the last dose given (slope).

25 In the atopic response, IgE is produced by B-cells in response to allergen stimulation. These antibodies coat mast cells by binding to the high affinity receptor for IgE (FcεRI). When a multivalent allergen binds to an IgE-coated mast cell, the cross-linking of adjacent IgEs by allergen initiates a

series of cellular events leading to the destabilisation of the cell membrane and release of inflammatory mediators. This results in mucosal inflammation, wheezing, coughing, sneezing and nasal blockage.

Atopy can be diagnosed by (i) a positive skin prick test in  
5 response to a common allergen; (ii) detecting the presence of specific serum IgE for allergen; or (iii) by detecting elevation of total serum IgE.

Genetic factors underlying a disease may be identified through localisation to particular chromosomal regions by genetic linkage. Genetic linkage is established by the study of families. It relies on matching the  
10 inheritance of disease with genetic polymorphisms of known localisation (known as "genetic markers"). In a complex disease such as asthma, genetic linkage will typically localise genes to within 10 - 20 Megabases (Mb) of DNA. A region of this size may contain 350 - 700 genes, and will be too large to permit immediate identification of the disease-causing gene.

15 Closer localisation of disease-causing genes may be accomplished by the detection of associations between particular alleles and the disease phenotype. Over short segments of DNA, distinctive alleles of the individual polymorphisms will show non-random association with alleles of neighbouring polymorphisms. This phenomenon, known as "linkage  
20 disequilibrium" occurs over 50-500 Kilobases (Kb) of DNA. Linkage disequilibrium may be detected by the study of individuals as well as by the study of families.

Disease-causing alleles will be in linkage disequilibrium with non-functional polymorphisms from the same chromosomal segment. It is  
25 therefore possible to detect allelic association with disease from particular chromosomal segments, without identifying the exact polymorphism and gene underlying the disease state.

The detection of allelic association may therefore give information as to disease susceptibility in a particular individual. Furthermore, allelic association is indicative of a disease-causing gene being present within 500 Kb of DNA in either direction from the allele (i.e. 1 Mb in total). Such a  
5 region may contain only 30 genes, within which the identification of the disease-causing gene is possible.

The presence of linkage disequilibrium also means that other polymorphisms may be anticipated to associate with disease, and that these additional polymorphisms will also be diagnostic of disease susceptibility in  
10 particular individuals.

Genetic associations with atopy have been demonstrated. WO 95/05481 discloses that variants of the gene encoding the  $\beta$ -subunit of the high-affinity receptor for IgE (Fc $\epsilon$ RI $\beta$ ) are associated with atopy. It teaches a method for diagnosing atopy which is based upon the  
15 demonstration of the presence or absence of one of two variants in a specific portion of the DNA sequence of the gene encoding Fc $\epsilon$ RI $\beta$ , located near the commencement of exon 6 of the Fc $\epsilon$ RI $\beta$  gene on chromosome 11. A further variant has also been found in which the unusual variant sequence is in the coding sequence for the C-terminal cytoplasmic tail of Fc $\epsilon$ RI $\beta$  (4).

20 Tumour Necrosis Factor (TNF) is a pro-inflammatory cytokine that is found in increased concentration in asthmatic airways (5). We have previously shown that polymorphisms within the TNF gene are associated with an increased risk of asthma (6).

The known polymorphisms do not account for all of the genetic  
25 factors which predispose to atopy. Identification of further genetic polymorphisms linked to atopy will allow the identification of individuals with susceptibility to atopy, for example children at risk before atopic disease has developed, with the potential for prevention of disease. The presence of



particular polymorphisms may predict the clinical course of disease (e.g. severe as opposed to mild) or the response to particular treatments. This diagnostic information will be of use to the healthcare, pharmaceutical and insurance industries.

5               We have previously established linkage of atopy to chromosome 13 (8). However, this finding is of no use in diagnosis.

              It has now been discovered that a genetic polymorphism known as D13S273\*4 on chromosome 13 is associated with atopy and can be used as a diagnostic tool.

10             The invention therefore provides a method for diagnosing an individual as being atopic, or as having a predisposition to atopy, which method comprises demonstrating in the individual the presence or absence of an allele which is associated with atopy, wherein the allele is situated at a locus in a region of chromosome 13 of up to 1 megabase in length, which  
15             region contains the locus D13S273.

              The 1 Mb region of chromosome 13 in which the D13S273 locus is situated flanks the D13S273 locus. Thus, the specific allele D13S273\*4, or other polymorphisms in the region which are associated with atopy, may be the subject of identification in the method according to the invention. Equally,  
20             two or more such alleles may be the subject of identification.

              Current diagnostic methods involving detection at the nucleic acid level normally comprise the steps of:

- (i) obtaining a suitable tissue sample from the individual;
- (ii) preparing from the tissue sample a nucleic acid sample;
- 25             (iii) analysing the nucleic acid sample for the presence or absence of the relevant nucleic acid sequence, such as a specific allele.

Preferably, an amplification step is performed prior to the analysis, such that the locus at which the allele is situated is amplified. A preferred amplification technique is the PCR, although any suitable method of nucleic acid amplification may be employed.

5 In further aspects, the invention provides a pair of oligonucleotide primers for amplification of an allele which is associated with asthma, which allele is situated at a locus in a region of chromosome 13 of up to 1 megabase in length, which region contains the locus D13S273; and an assay kit comprising the pair of oligonucleotide primers.

10 The specific allele for identification may take the form of microsatellite repeats, which are nucleotide sequences containing short, repeated nucleotide motifs, usually a dinucleotide or a trinucleotide motif. A pair of primers which hybridize under suitably stringent conditions, to sequences at a position on either side of the microsatellite repeats, may be  
15 used to amplify the microsatellite repeats by PCR. Differences in the number of repeats are recognised by size differences in the PCR products. An allele which has a specified number of repeats and therefore a known size can thus be identified. D13S273\*4 is one such allele.

The primers employed in the method comprise nucleic acid  
20 sequences which are complementary to, or substantially complementary to unique sequences either side of the microsatellite repeats, such that only the relevant polymorphic region of the genome is amplified. The conditions under which the amplification is performed are gauged such that specific hybridization of the primers to the flanking sequences occurs and non-specific  
25 hybridization is avoided. The hybridization conditions are suitably stringent for that purpose. Standard techniques can be used to identify an appropriate set of reaction conditions.

Typically, the PCR products are detected by means of a detectable label attached to one of the PCR primers. Alternatively another form of labeling may be used such as a labeled sequence specific probe which hybridizes to the amplified sequences. The label may be a fluorescent or other label. The PCR products are subjected to size determination, typically involving size-separation for example by gel electrophoresis, and the presence or absence of the allele of interest is determined.

It will be evident that the invention is not limited with regard to the manner in which the presence or absence of the allele of interest is determined. The labeling, detection, separation or any other aspect of the method as described here may be replaced by other suitable known techniques and reagents.

The allele for identification may be an allele other than D13S273\*4 which is in linkage disequilibrium with D13S273\*4 and is associated with asthma. This includes alleles of both functional and non-functional polymorphisms. Functional polymorphisms include polymorphisms within genes, usually within coding sequences of genes. Non-functional polymorphisms are polymorphisms which do not themselves cause the disease.

This invention will now be further described in the Examples section which follows. The Examples are intended to be illustrative and do not limit the scope of the invention in any way.

## EXAMPLES

### 25 Description of Laboratory Testing

#### **Subjects:**

Two panels of subjects have been studied.

Panel A consisted of 80 nuclear families sub-selected from an Australian population sample of 230 families (8). The panel contained a total of 203 offspring forming 172 sib-pairs. Fifty-two % of the children were atopic.

Panel B consisted of 77 nuclear and extended families recruited from atopy and allergy clinics in the United Kingdom. These families contained 215 offspring forming 268 sib-pairs. Sixty-one % of the children were atopic.

### ***Phenotypes***

Skin tests to House Dust Mite (HDM) and mixed grass pollen (less the response of negative controls), specific IgE titres to HDM and Timothy Grass, and the total serum IgE were measured. A "Skin Test Index (STI)" was calculated as the sum of the prick skin test results to HDM and grass mix. "Atopy" was defined as a STI > 5mm, or a RAST score to HDM and Timothy Grass > 2, or a total serum IgE > the 7th decile of the age-corrected population.

### ***Genotypes***

The microsatellite markers were typed by semi-automated fluorescent methods, as described previously (8).

The polymerase chain reaction primer sequences for the marker D13S273 were as follows:

D13S273            5' CTG NGG CAA AAA CAA CTC TT (SEQ ID NO: 1)

UD13S273           5' ATC TGT ATG TCC TCC TTT CAA TG (SEQ ID NO: 2)

The polymerase chain reaction conditions were as follows:

The reaction volumes were 10 $\mu$ l, containing 50ng of genomic DNA, 200mM dNTPs, 1 x NH<sub>4</sub><sup>+</sup> buffer, 50ng oligonucleotide primers (forward labelled fluorescently), 0.5 to 3.0mM MgCl<sub>2</sub> and 0.2U Taq polymerase. Cycling

conditions were 1 min at 95°C, 1min at 55°C and 45s at 72°C; 28 cycles were used. PCRs were performed on an Hybaid Omnigene thermal cycler.

Electrophoresis and allele scoring were as follows:

- 5 PCR products were mixed with a size standard (GS350 TAM) in loading buffer (80% (v/v) formamide, 20% (v/v) 50mM EDTA, 0.1% (w/v) blue dextran). Samples were denatured at 95°C for 4min immediately prior to loading onto a 6% polyacrylamide gel and were electrophoresed at 800v for 6h on an Applied Biosystems (ABI) 373 DNA sequencer. Allele sizes were assigned using the
- 10 ABI GENESCAN and ABI GENOTYPER software.

### **Association Analysis**

Association was tested against the phenotype of atopy by the Transmission Disequilibrium Test.

15

### **Results**

- Association with the atopy phenotype was seen in each panel for allele 4 of D13S273 (D13S273\*4). This allele is 238 base pairs in size, using the primers described above. (Other primers can be designed and their
- 20 amplification product size determined for D13S273\*4, using known sequence information (9).) The results of TDT testing were as follows:

	Panel A			Panel B			combined		
	T	N	p	T	N	p	T	N	p
Maternal	22	24	.0081	36	18	.0099	58	26	.00048
Paternal	13	24	ns	25	28	ns	38	52	ns

The results indicate that D13S273\*4 shows a strong reproducible association with atopy in two diverse panels of subjects. It may therefore be inferred that a gene influencing atopy is present within 500 kilobases in either direction of D13S273.

5

## REFERENCES

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CLAIMS

1. A method for diagnosing an individual as being atopic, or as having a predisposition to atopy, which method comprises demonstrating in a nucleic acid sample taken from an individual the presence or absence of an allele which is associated with atopy, wherein the allele is situated at a locus in a region of chromosome 13 of up to 1 megabase in length, which region contains the locus D13S273, the presence of the allele D13S273\*4 being indicative of a predisposition to asthma.
2. The method according to claim 1, wherein the method comprises the steps of:
  - (i) obtaining a suitable tissue sample from the individual;
  - (ii) preparing from the tissue sample a nucleic acid sample;
  - (iii) analysing the nucleic acid sample for the presence or absence of the allele.
3. The method according to claim 2, wherein prior to analysis, the locus at which the allele is situated is amplified.
4. The method according to claim 3, wherein the amplification is by the PCR.
5. The method according to any one of the claims 1 to 4, wherein the locus at which the allele is situated comprises microsatellite repeats of variable lengths.
6. The method according to claim 4 or claim 5, wherein amplification is performed using a pair of primers each of which hybridise under suitably stringent conditions to a region either side of the microsatellite repeats.



7. The method according to any one of claims 1 to 6, wherein the allele for identification is D13S273\*4.
8. The method according to any one of claims 3 to 7, wherein the analysis is carried out by size separation of amplification products.
9. The method according to claim 7, wherein the primers in the pair of primers comprise the oligonucleotide sequences identified by SEQ ID NO: 1 and SEQ ID NO: 2 or substantially similar sequences.
10. A pair of oligonucleotide primers for amplification of an allele which is associated with atopy, which allele is situated at a locus in a region of chromosome 13 of up to 1 megabase in length, which region contains the locus D13S273, but not including the region containing the locus D13S153.
11. The pair of oligonucleotide primers according to claim 10, one of which is labeled with a detectable marker.
12. The pair of oligonucleotides according to claim 10 or claim 11, capable of hybridising under suitably stringent conditions to a region either side of a region of microsatellite repeats at D13S273.
13. The pair of oligonucleotide primers according to claim 12, comprising the oligonucleotide sequences identified by SEQ ID NO: 1 and SEQ ID NO: 2 or similar sequences.
14. An assay kit which comprises the pair of oligonucleotide primers according to any one of claims 10 to 13.

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Rev. 11-3/98

Effective March 1998

## DECLARATION AND POWER OF ATTORNEY FOR U.S. PATENT APPLICATION

(X) Original () Supplemental () Substitute () PCT () DESIGN

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; that I verily believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Title: POLYMORPHISM III: LINKAGE OF ATOPY TO A LOCUS ON CHROMOSOME 13

of which is described and claimed in:

() the attached specification, or

(X) the specification in application Serial No. 09/647,330, filed September 27, 2000, and with amendments through (if applicable), or

() the specification in International Application No. , filed , and as amended on (if applicable).

I hereby state that I have reviewed and understand the content of the above-identified specification, including the claims, as amended by any amendment(s) referred to above.

I acknowledge my duty to disclose to the Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim priority benefits under Title 35, United States Code, §119 (and §172 if this application is for a Design) of any application(s) for patent or inventor's certificate listed below and have also identified below any application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

COUNTRY	APPLICATION NO.	DATE OF FILING	PRIORITY CLAIMED
Great Britain	9806656.6	March 27, 1998	Yes

I hereby claim the benefit under Title 35, United States Code §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose information material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

APPLICATION SERIAL NO.	U.S. FILING DATE	STATUS: PATENTED, PENDING, ABANDONED

And I hereby appoint Michael R. Davis, Reg. No. 25,134; Matthew M. Jacob, Reg. No. 25,154; Jeffrey Nolon, Reg. No. 25,408; Warren M. Cheek, Jr., Reg. No. 33,367; Nils Pedersen, Reg. No. 33,145; and Charles R. Watts, Reg. No. 33,142 who together constitute the firm of WENDEROTH, LIND & PONACK, L.L.P., jointly and severally, attorneys to prosecute this application and to transact all business in the U.S. Patent and Trademark Office connected therewith.

I hereby authorize the U.S. attorneys named herein to accept and follow instructions from Kilburn and Strode as to any action to be taken in the U.S. Patent and Trademark Office regarding this application without direct communication between the U.S. attorneys and myself. In the event of a change in the persons from whom instructions may be taken, the U.S. attorneys named herein will be so notified by me.

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I further declare that all statements made herein of my own knowledge are true, and that all statements on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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The above application may be more particularly identified as follows:

U.S. Application Serial No. 09/647,330 Filing Date September 27, 2000

Applicant Reference Number P30626US/KVC/PSCE Auy Docket No. 2000-1719

Title of Invention POLYMORPHISM III: LINKAGE OF ATOPY TO A LOCUS ON CHROMOSOME 13